Claim 1 has been amended to define the claimed inhibitor as including a polypeptide backbone (page 9, lines 14-15), containing isosters that *mimic* the transition state of the aspartic acid protease to be inhibited (page 9, lines 15-16, and which have different orientations (i.e., not a single isoster having a single orientation) (see page 4, lines 31-32). This is shown diagrammatically on page 10, lines 10-20, compared to the prior art inhibitors having a single isoster, as shown diagrammatically on page 9, lines 14-29.

The present invention is directed to aspartic protease inhibitors possessing "modules" (isosteres) that mimic the scissile bond normally cleaved by the core structure of aspartyl proteases. These inhibitors are designed and constructed based on a well known correlation between the structure and mechanism of action of the well known aspartic protease family of enzymes. An isostere represents a specific arrangement of atoms that mimic the substrate peptide bond that is normally cleaved by the catalytic core of the targeted protease. In order to "present" the peptide bond *mimic* (the isostere) to the protease, the inhibitor binds the protease and the isostere must "fit" into the catalytic core of the protease.

As discussed repeatedly throughout the specification, isoster inhibitors of aspartic acid proteases are well known, well characterized, and widely tested in patients. See page 3, line 6-page 4, line 8; Figures 1a-1d; see also page 9, line 14-page 10, line 4. There are numerous disclosures of such inhibitors in the scientific literature as well as patents – see, for example, U.S. Patent No.s 6,121,417 and 5,587,514.

The invention is not the discovery that one can make an inhibitor to an aspartic acid protease by inserting an isoster into the compound, but that one can insert two isosters and the

compound will still bind and be able to inhibit. It was not predictable that one could do this: it was equally predictable that one would create instability and decrease binding affinity to the point that the inhibitor would be useless. Binding affinity is critical to efficacy. See, for example, the discussion on page 11, at lines 1-24.

**Rejection Under 35 U.S.C. § 112, first paragraph**

Claims 1-4, 6-10, and 12 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Applicants respectfully traverse this rejection.

The Examiner states that the Applicant's specification provides a transition state isostere represented by the formula -CH(OH)-$CH_2$- as the only example of a transition state isostere. This is simply not true. The very same paragraph in which -CH(OH)-$CH_2$- is disclosed, provides other examples of isosteres, including hydroxyethylamine, phosphinate, and reduced amide (see page 4, lines 1-8). See also the structures in Figures 1a-1d, all of which contain different isosters, although only one per compound. Given that the *de novo* design of protease inhibiting compounds requires one to characterize the target protease as a member of a particular class, for example, serine, cysteine, metallo, or aspartyl, and that known isosteres exist as single isostere compounds for the inhibition of aspartic proteases, the design and construction of an inhibitor harboring two or more isosteres can be accomplished without undue experimentation. One working example is provided in the specification (UIC-98-056), but many other side chain modifications that could be made are also described. Based upon the common core structure of aspartyl proteases, the inhibitors are structurally defined in terms of *size, physical and chemical properties*. The applicants have clearly provided an enabling disclosure for the design and

construction of two isostere inhibitory compounds that are defined by the size, physical properties, and chemical properties of the targeted aspartyl protease. Even if one was not familiar with the structural properties of a targeted protease, the amino acid sequence of the protease can be easily inserted into any number of commercially available computer programs and the structural features of the protease determined. The aspartic acid protease class of enzymes has been characterized to the extent that the types and arrangement of binding interactions available in the core are known. Inhibitory drug design relies upon such interactions to provide specificity and affinity. These interactions and the local environment provided by the known amino acids of the core, including hydrogen bond acceptors and donors, electrostatic interactions and the hydrophobic environment, all contribute to the core structure, size and geometry. The structure of the inhibitor is clearly limited based on the requirement for it to bind adjacent to the peptide scissile peptide bond in the core of the targeted enzyme.

Claims 1-4, 6-10, and 12 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

To facilitate prosecution, the independent claim to the inhibitor has been amended to incorporate definitions of the chemical nature of the inhibitor. The claimed isosteres are *part* of the overall structure of the inhibitor. The structures (for example, a polypeptide backbone) emanating from the isosteres aid in providing stability and proper alignment with the subsites

present within the targeted aspartic acid protease. As noted above, there are other examples of isosteres taught in the present specification. The well known and characterized enzymatic pocket of the targeted aspartic protease is the controlling factor in dictating the structure of the claimed isostere compounds. Since the core structure of the aspartyl class of proteases is what defines the aspartyl proteases to be grouped together, the physical and chemical properties are not so different as to effect the design of a class of inhibitors based upon the conserved characteristics of the enzymatic core.

**Rejection Under 35 U.S.C. § 112, second paragraph**

Claims 1-4, 6-10, and 12 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

The Examiner points to page 3, line 26, as providing ambiguity to the term "transition state isostere". It should be noted that line 26 is a statement referring to the Marciniszyn *et al.* study discussed at lines 23-24, of page 3. As noted later in the same paragraph (see lines 1-8, page 4), other types of transition state isosteres may be used in aspartic protease inhibitors. Regardless of the type of transition state isostere previously used, in all cases, they have been used as *single* transition state isosteres to inhibit aspartic proteases such as HIVPr. Applicants are claiming *inhibitors comprising* two or more transition-state isosteres. Isosteres are known. Many drug inhibitors possess an isostere (or "module") that mimics the scissile bond of the substrate that is normally cleaved by the targeted protease. Single isostere compounds are not new. Single isostere inhibitors have been so widely used that there is an increased pressure on

the targeted protease to mutate and elude the specific targeting of the inhibitor harboring the isostere. The novelty of the presently claimed composition resides in inhibitors harboring two or more isosteres and the fact that these inhibitors have an increased efficacy in inhibiting the activity of aspartic proteases by decreasing the pathogen's ability to become resistant to the protease inhibitor. The invention, the design of aspartic protease inhibitors less vulnerable to mutation-resistance, is based on placing two or more isosteres into the backbone (see page 10, lines 7-20). As further discussed in the Appeal Brief mailed on September 26, 2001, the common core structure of this particular class of proteases, to which the two or more isostere containing inhibitors bind and inhibit activity, structurally defines the inhibitor in terms of size, physical and chemical properties.

**Rejection Under 35 U.S.C. § 102**

Claims 1, 2, 4, and 6 were rejected under 35 U.S.C. § 102(b) as being anticipated by Takatori (JP 09208450, CA 127:238926), Sugiura (CA 127:210184), and Kono (JP 09143044, CA 127:39539). Applicants respectfully traverse this rejection to the extent that it is applied to the claims as amended.

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

None of Takatori, Sugiura or Kono disclose aspartic acid protease inhibitors containing two isosters. Therefore none of the prior art disclose the claimed subject matter.

Except in hindsight based on the applicant's disclosure, *there is no suggestion to one of ordinary skill in the art to either combine, or use singly, the cited references to derive applicant's claimed composition for aspartic protease inhibition.*

Allowance of claims 1, 2, and 4-12 is respectfully solicited.

Respectfully submitted,

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Date: March 18, 2002

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U.S.S.N. 09/506,988
Filed: February 18, 2000
**CLEAN VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121**

## Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the Assistant Commissioner for Patents, Washington, D.C. 20231 on the date shown below.

Patrea L. Pabst

Date: March 18, 2002

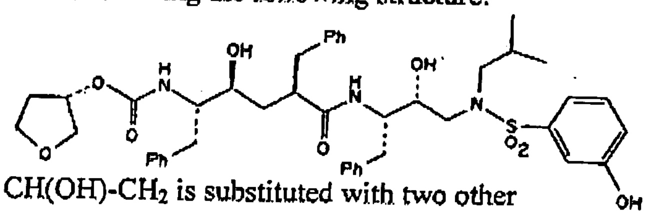
**Marked up Copy of Claims as Amended**

1. (twice amended) [An] A polypeptide aspartic acid protease inhibitor comprising two or more transition-state isosteres in the polypeptide backbone, which have different orientations that mimic the transition state of the aspartic acid protease, and bind to different subsite binding pockets in the aspartic acid protease.

2. The inhibitor of claim 1 wherein the transition-state isostere is $-CH(OH)-CH_2-$.

4. (Amended) The composition of claim 1 wherein the aspartic acid protease inhibitor is an HIV protease inhibitor.

5. The inhibitor of claim 1 which is UIC-98-056 having the following structure:



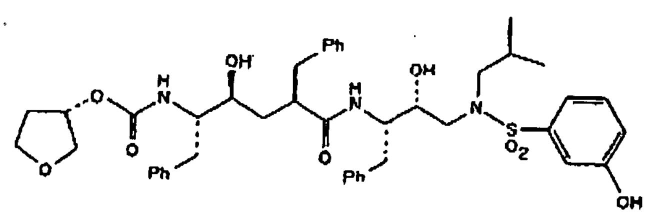
6. The inhibitor of claim 2 wherein the $CH(OH)-CH_2$ is substituted with two other kinds of isosteres.

7. (Amended) A method for treating a patient infected with a pathogen expressing an aspartic acid protease comprising the oral administration of an aspartic acid protease inhibitor comprising two or more transition-state isosteres.

8. The method of claim 7 wherein the transition-state isostere is $CH(OH)-CH_2-$.

10. (Amended) The method of claim 7 wherein the protease inhibitor inhibits HIV protease.

11. The method of claim 10 wherein the inhibitor is UIC-98-056 having the following structure:



12. The method of claim 8 wherein the $CH(OH)$-$CH_2$ is substituted with two other kinds of isosteres.

U.S.S.N. 09/506,988
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CLEAN VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

**Clean Version of Amended Claims**

**Pursuant to 37 C.F.R. § 1.121(c)(1)(*ii*)**

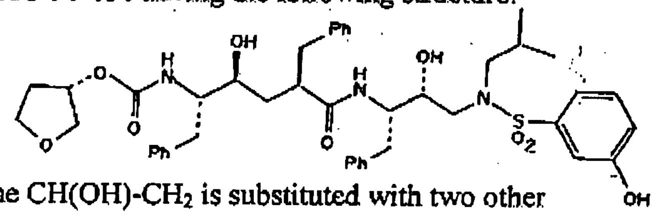
D1

1. (twice amended) A polypeptide aspartic acid protease inhibitor comprising two or more transition-state isosteres in the polypeptide backbone, which have different orientations that mimic the transition state of the aspartic acid protease, and bind to different subsite binding pockets in the aspartic acid protease.

2. The inhibitor of claim 1 wherein the transition-state isostere is -CH(OH)-$CH_2$-.

4. (Amended) The composition of claim 1 wherein the aspartic acid protease inhibitor is an HIV protease inhibitor.

5. The inhibitor of claim 1 which is UIC-98-056 having the following structure:



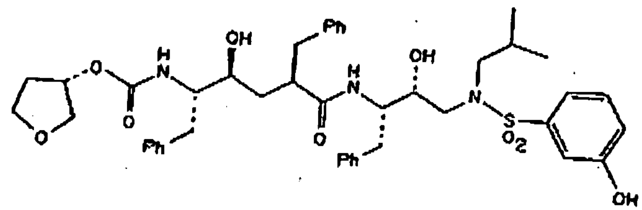

6. The inhibitor of claim 2 wherein the CH(OH)-$CH_2$ is substituted with two other kinds of isosteres.

7. (Amended) A method for treating a patient infected with a pathogen expressing an aspartic acid protease comprising the oral administration of an aspartic acid protease inhibitor comprising two or more transition-state isosteres.

8. The method of claim 7 wherein the transition-state isostere is CH(OH)-$CH_2$-.

10. (Amended) The method of claim 7 wherein the protease inhibitor inhibits HIV protease.

11. The method of claim 10 wherein the inhibitor is UIC-98-056 having the following structure:



12. The method of claim 8 wherein the $CH(OH)$-$CH_2$ is substituted with two other kinds of isosteres.